

## In Utero Diagnosis of Long QT Syndrome by Magnetocardiography

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**Background**—The electrophysiology of long QT syndrome (LQTS) in utero is virtually unstudied. Our goal here was to evaluate the efficacy of fetal magnetocardiography (fMCG) for diagnosis and prognosis of fetuses at risk of LQTS.

**Methods and Results**—We reviewed the pre/postnatal medical records of 30 fetuses referred for fMCG because of a family history of LQTS (n=17); neonatal/childhood sudden cardiac death (n=3), or presentation of prenatal LQTS rhythms (n=12): 2° atrioventricular block, ventricular tachycardia, heart rate < 3<sup>rd</sup> percentile. We evaluated heart rate and reactivity, cardiac time intervals, T-wave characteristics, and initiation/termination of Torsade de Pointes, and compared these with neonatal ECG findings. After birth, subjects were tested for LQTS mutations. Based on accepted clinical criteria, 21 subjects (70%; 9 KCNQ1, 5 KCNH2, 2 SCN5A, 2 other, 3 untested) had LQTS. Using a threshold of corrected QT=490 ms, fMCG accurately identified LQTS fetuses with 89% (24/27) sensitivity and 89% (8/9) specificity in 36 sessions. Four fetuses (2 KCNH2 and 2 SCN5A), all with corrected QT ≥ 620 ms, had frequent episodes of Torsade de Pointes, which were present 22–79% of the time. Although some episodes initiated with a long-short sequence, most initiations showed QRS aberrancy and a notable lack of pause dependency. T-wave alternans was strongly associated with severe LQTS phenotype.

**Conclusions**—Corrected QT prolongation (≥490 ms) assessed by fMCG accurately identified LQTS in utero; extreme corrected QT prolongation (≥620 ms) predicted Torsade de Pointes. fMCG can play a critical role in the diagnosis and management of fetuses at risk of LQTS. (*Circulation*. 2013;128:2183-2191.)

**Key Words:** alternan ■ arrhythmias, cardiac ■ fetus ■ long QT syndrome  
■ magnetocardiography ■ torsades de pointes

Long QT syndrome (LQTS) and its signature rhythm, Torsades de Pointes (TdP), have been diagnosed in utero by magnetocardiography (MCG) and, in a few cases, successfully treated before birth.<sup>1-6</sup> The findings of a prolonged corrected QT (QTc) interval and characteristic polymorphic ventricular tachycardia are well described in case reports, yet the accuracy of MCG for diagnosing LQTS in a sizable population of at-risk fetuses has not been studied. In addition, little is known of the electrophysiology and natural history of LQTS before birth, how repolarization characteristics and LQTS rhythms compare before and after birth, or whether there are electrophysiological harbingers of severe prenatal LQTS phenotypes.

### Clinical Perspective on p 2191

The purposes of this study were 2-fold. First, in a large cohort of fetuses at risk for LQTS we tested the ability of fetal MCG to distinguish fetuses that had LQTS from those that did not. Second, we compared the cardiac intervals, rhythms, and

repolarization characteristics before birth (by MCG) and after birth (by ECG) in the same subjects. We expected that subjects with the longest QTc intervals would manifest the most severe LQTS rhythm phenotypes.

### Methods

#### Subject Cohort

A cohort of 30 subjects was recruited from subjects referred for fetal MCG to the Biomagnetism Laboratories in the Department of Medical Physics at the University of Wisconsin – Madison (n=23), the Department of Pediatrics at the University of Tsukuba, Tsukuba, Japan (n=6) and the Department of Pediatric Cardiology at the National Cerebral and Cardiovascular Center, Osaka, Japan (n=1) from 1996 to 2012. Inclusion criteria were (1) a positive family history of LQTS or unexplained sudden death of a sibling during infancy or childhood or (2) findings of an LQTS rhythm: low fetal heart rate (fHR), defined as heart rate ≤3<sup>rd</sup> percentile for gestational age<sup>7</sup>; ventricular tachycardia (VT; atrioventricular [AV] dissociation and faster ventricular than atrial rate); or anti-Ro/La antibody-negative second-degree atrioventricular block (2° AV block) with a structurally normal heart diagnosed by fetal echocardiography. We

Received May 6, 2013; accepted September 10, 2013.

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.113.004840

reviewed the pre- and postnatal medical records, including results of fetal echocardiograms, postnatal ECG, and postnatal genetic testing. The research was approved by the Institutional Review Boards at the participating centers.

### Fetal MCG Evaluation

Fetal MCGs were performed using a 37-channel biomagnetometer (Magnes, 4D Neuroimaging, Inc.) at the University of Wisconsin-Madison and 64-channel biomagnetometers (MC-6400, Hitachi Ltd.) at both the University of Tsukuba and the National Cerebral and Cardiovascular Center in Osaka. All of the recordings were made in a magnetically shielded room. For each subject, continuous MCG data were collected in 5- to 10-minute runs over a period of 10 minutes to 1.5 hour. The probe was positioned on the maternal abdomen, proximal to the fetal heart. Using autocorrelation to detect QRS complexes, ventricular fHR tracings were computed from the RR intervals, and actograms (tracings of fetal activity derived from movement-related changes in signal amplitude) were derived from the instantaneous QRS amplitudes.<sup>8</sup> Approximately 50 consecutive fetal complexes were averaged during periods of fetal quiescence to increase the signal-to-noise ratio, before measurement of the fetal (f) cardiac time intervals—fQRS, fQT, and fQTc.

Actocardiograms were examined to identify movement-related changes in fetal rhythm and fHR (ie, fHR reactivity). Reactivity was assessed in fetuses at  $\geq 28$  weeks' gestation; before this time it cannot be reliably assessed. At 28–32 weeks, normal reactivity is defined as fHR accelerations  $\geq 10$  bpm, lasting  $\geq 10$  s that occur in association with fetal movement. After 32 weeks', the accelerations increase in amplitude and duration to  $>15$  bpm and  $>15$  s, respectively.<sup>9</sup>

Fetal rhythm was assessed from continuous rhythm recordings, after removal of maternal interference. We defined 2° atrioventricular block as a regular P-P interval with conduction of every other atrial beat, and TdP as paroxysms of a wide complex rhythm with a variable QRS morphology that exceeded the baseline ventricular rate. We described the QRS morphology as narrow ( $< 95^{\text{th}}$  % for gestational age) or wide ( $> 95^{\text{th}}$  %).<sup>10</sup> Because P-waves were not always visible on the tracings, we made the assumption that a rhythm with a regular R-R interval, a narrow QRS, and a rate of 90–160 bpm was sinus rhythm. We also inspected the recordings for beat-to-beat changes in QRS and T-wave morphology (ie, alternans).

### Postnatal Evaluation: ECG, Rhythm, and Genetic Testing

After birth, neonatal (n) cardiac intervals (nQRS, nQT, and nQTc), rhythm, and T-wave characteristics were assessed by 12-lead ECG performed within the first 48 hours of life. Subjects were tested for mutations in LQTS-susceptibility genes (LQT1, 2, 3, 5, and 8) by commercial laboratories (Familon, Transgenomic Inc, New Haven, CT; GeneDx, Gaithersburg, MD). If the family history was positive for LQTS, we tested the newborn only for the family mutation. Similarly, if a newborn was found to have an LQTS mutation, first degree relatives were evaluated by ECG and, when appropriate, genetic testing. LQTS was diagnosed by the presence of a mutation in an LQTS-susceptibility gene or, in the absence of such a mutation, the clinical findings of TdP or neonatal QTc  $> 490$  ms. We compared the cardiac intervals, rhythm, and repolarization characteristics between individuals before and after birth, and between different LQTS mutation types. Finally, we sought fMCG characteristics predictive of fetal/neonatal TdP.

### Statistical Analysis

The performance of fQTc and fQT for detection of LQTS were assessed using receiver operating characteristic curves. The receiver operating characteristic curves were computed 2 ways: first using data from all sessions and second using data from just the first session of each subject, to remove the effects of within-subject correlation. We reported descriptive statistics (mean $\pm$ SD) for continuous data. Within subjects, differences between fetal and neonatal cardiac time

intervals and heart rate were tested by dependent *t* test. The degree of correlation between QTc determined by fMCG and postnatal ECG was assessed by linear correlation analysis. Differences between LQTS and non-LQTS subjects were tested by *t* test. For subjects with multiple sessions only the first session was used. Because of the small sample size of subjects with TdP, nonparametric statistics (Mann-Whitney test and Kruskal-Wallis test) were used to compare differences in continuous variables for T-wave alternans (TWA), QTc, and LQTS rhythms to determine which fMCG features predicted fetal/neonatal TdP. A 2-tailed *P* value of  $\leq 0.05$  was considered statistically significant. Analyses were performed with SPSS software (release 19.0, SPSS-IBM, Chicago, IL).

## Results

### Subject Cohort

The subject cohort is shown in the Table, which divides the subjects into 2 groups based on LQTS diagnosis. Between 1996 and 2012, 29 pregnant women during 30 pregnancies were referred for 36 fMCG studies (4 subjects had 2 studies, 1 subject had 3) at 19–38 (mean  $29.5\pm 5.2$ ) weeks' gestation because of risk factors for fetal LQTS. One mother was evaluated for 2 pregnancies that were counted separately (#4 and #20). Twenty subjects were studied because of a family history of either a known LQTS gene ( $n=17$ ) or the neonatal/childhood sudden death of a sibling ( $n=3$ ), and were referred at  $19.1\pm 4.8$  weeks. Of these, one had 2° AV block and one had premature ventricular contractions (PVCs) at the time of referral. The other 10 fetuses were studied because of suspicious rhythms—low fHR in sinus rhythm ( $n=6$ ), 2° AV block ( $n=1$ ), VT ( $n=1$ ), 2° AV block + VT ( $n=2$ )—and were referred at  $29.8\pm 5.2$  weeks.

In the Table, Group 1 consists of the 21 fetuses found to have LQTS: 17 with a mutation in an LQTS susceptibility gene, 1 mutation negative subject with nQTc of 540 ms, and 3 that declined genetic testing, but had nQTc  $> 490$  ms and a family history of LQTS. The QTc intervals of the latter 4 subjects remained prolonged ( $>490$  ms) for months to years after birth (data not shown). Remarkably, only 57% (12) of these fetuses had a family history of LQTS (10 maternal, 2 paternal). Group 2 consists of 9 fetuses found not to have LQTS, based on absence of mutation and normal postnatal QTc. Of these, 8 were referred because of a family history of LQTS or the sudden death of a sibling during infancy or childhood, and 1 had low fHR in sinus rhythm.

### Fetal MCG

#### Fetal Cardiac Intervals and fHR Reactivity

The fQTc intervals are indicated on the averaged waveforms in Figure 1A and 1B. As expected, fQTc was much longer in Group 1 ( $565\pm 65$  ms) than in Group 2 ( $421\pm 54$  ms;  $P<0.0001$ ; Table). Furthermore, the 4 subjects with fetal TdP had QTc 628–692 ms. Their mean QTc ( $660\pm 31$  ms) was significantly longer than that of the Group 1 subjects without TdP ( $549\pm 55$ ms;  $P=0.003$ ). A notable feature of the data of the Group 1 subjects (Figure 1) is the late-peaking morphology of T-waves, which show T-wave humps in some subjects. The  $QT_{\text{peak}}/QT$  ratio was  $0.88\pm 0.05$  for Group 1 and  $0.73\pm 0.12$  ( $p<0.0001$ ) for Group 2, where  $QT_{\text{peak}}$  is the interval from the beginning of the QRS complex to the peak of the T-wave.

**Table. Fetal Cohort of 30 Subjects at Risk for LQTS**

ID	GA fMCG (wks)	Reason for fMCG	fQTc (ms)	nQTc (ms)	fHR (bpm)	nHR (bpm)	fRhythm		TWA	fHR React	LQT mutation
							Echo	fMCG			
Group 1: LQTS subjects (n= 21)											
1	37	FH	552	590	110	104	sinus	sinus	N	N	KCNQ1 A341V
2	29	FH	550	506	130	140	sinus	sinus	N	Y	KCNH2 W1001X
3	38	FH	445	570	144	115	sinus	sinus	N	Y	Not tested
4	36	FH	542	500	123	114	sinus	sinus	N	Y	KCNQ1 R594Q
5	31	FH	563	522	120	126	sinus	sinus	N	N	KCNQ1 R190W
6*	28	arrhyt	680	700	105	100	VT 2°AVB	TdP 2°AVB	N	—	KCNH2 G628S
7†	36	arrhyt	528	554	117	116	sinus	sinus	N	Y	KCNQ1 R539W
8†	23	arrhyt	449	488	119	110	sinus	sinus	N	—	KCNQ1 R258C
9*	25	arrhyt	559	582	113	129	sinus	sinus	N	—	KCNQ1V110fs132X
9A	34		541		111		sinus	sinus	N	Y	
10	35	arrhyt	588	540	106	98	sinus	sinus	Y	Y	uncharacterized
11*§	27	arrhyt	633	580	103	119	sinus	2° AVB	Y	—	CALM2
11A	32		616		100		sinus	sinus	Y	Y	
12†	26	arrhyt	522	462	126	140	2°AVB	sinus	N	—	KCNQ1 G314D
13	36	FH	569	560	115	125	sinus	sinus	N	—	Not tested
14	36	FH+arrhyt	550	550	90	70	2°AVB	2° AVB	N	N	Not tested
15*	31	arrhyt	692	540	106	110	VT, 2° AVB	TdP, 2°AVB	Y	—	SCN5A R1623Q
16*‡	21	arrhyt	628	—	140	—	VT	TdP	Y	—	SCN5A L409P
17	26	FH+ arrhyt	632	492	129	125	sinus	sinus	Y	—	KCNH2 A614V
17A	33		598		120		PVC	PVC	Y	Y	
18	34	FH	639	568	125	109	sinus	TdP, 2° AVB	Y	Y	KCNH2 T613K
19	25	FH	548	544	125	101	sinus	sinus	N	—	KCNQ1 R594Q
20	28	FH	547	544	112	101	sinus	sinus	N	N	KCNQ1 R594Q
20A	34		524		112		sinus	sinus	N	N	
21	27	FH	413	520	138	125	sinus	sinus	N	--	KCNH2
21A	29		569		132		sinus	sinus	N	N	L1064fsX1068
21B	34		586		138		sinus	sinus	N	N	
Mean QTc 565.3±65.3 ( $P<0.0001$ ) fHR 118.9±13.3 ( $P<0.0001$ )											
Group 2: non-LQTS subjects (n= 9)											
22	31	arrhyt	524	442	125	125	sinus	sinus	N	Y	No mutation
23	24	FH	396	436	132	138	sinus	sinus	N	—	No mutation
24	28	FH	453	414	155	164	sinus	sinus	N	Y	No mutation
25	20	FH	359	452	146	126	sinus	sinus	N	—	No mutation
26	23	FH	459	432	147	150	sinus	sinus	N	—	No mutation
27	24	FH	382	388	147	114	sinus	sinus	N	—	No mutation
28	26	FH	448	420	134	126	sinus	sinus	N	—	No mutation
29	19	FH	373	438	138	172	sinus	sinus	N	—	No mutation
30	30	FH	391	473	145	104	sinus	sinus	N	Y	No mutation
Mean QTc 420.6±53.6 fHR 141.0±9.4.											

arrhyt indicates arrhythmia; AVB, atrioventricular block; FH, family history; fHR, fetal heart rate (sinus rate); fMCG, fetal magnetocardiogram; fQTc, fetal corrected QT interval; fRhythm, fetal rhythm; GA, gestational age; ms, milliseconds; N, no; nHR, neonatal heart rate; nQTc, neonatal corrected QT interval; PVC, premature ventricular contraction; React, reactivity; TdP, Torsades de Pointes; TWA, T-wave alternans; VT, ventricular tachycardia; wks, weeks; and Y, yes.

\*De novo mutation.

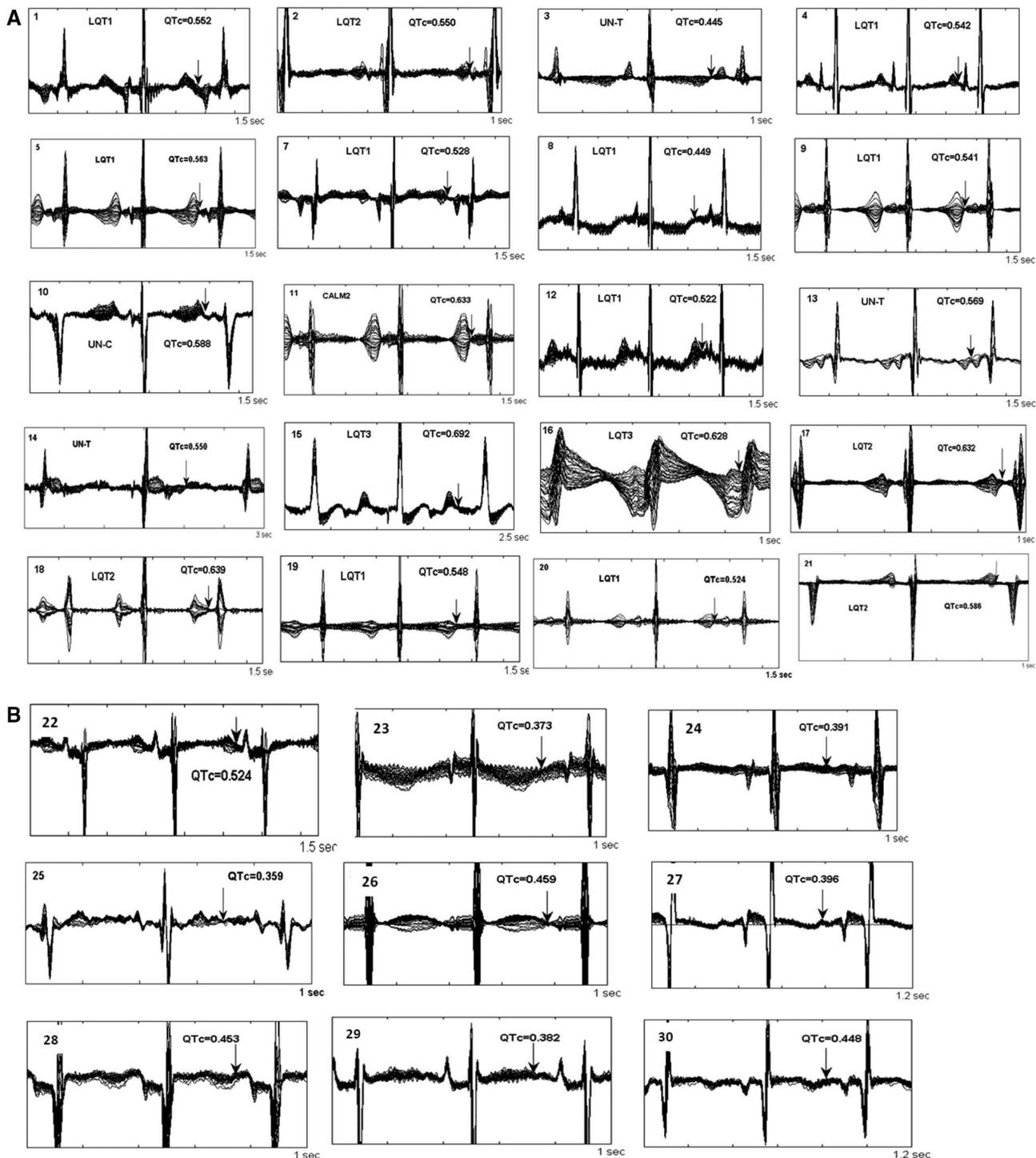
†Fetus was proband.

‡Elective termination.

§Subject had postnatal Torsades de Pointes and cardiac arrest.

The accuracy of fQTc for detection of LQTS was assessed using a receiver operating characteristic curve (not shown). Using data from all sessions, the best performance,

corresponding to the point closest to the upper left corner of the graph, was obtained for a threshold of  $460 < QTc < 520$  ms, which yielded sensitivity 89% and specificity 89%. Using

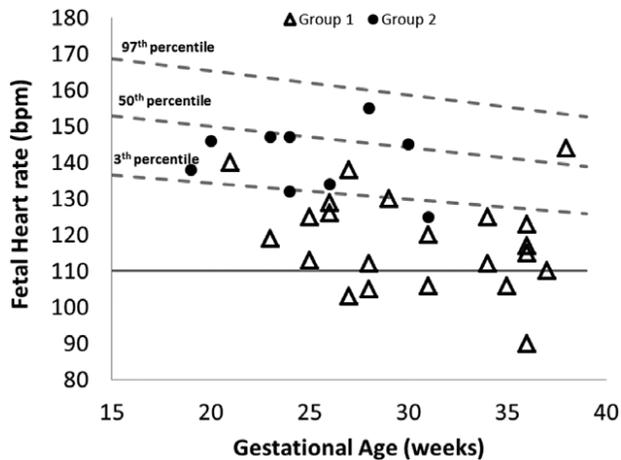


**Figure 1.** Signal-averaged fMCG waveforms, showing QTc duration during sinus rhythm in the cohort of 30 fetuses. In each tracing, the signals from all channels are superimposed. Time is shown on the x axis and was adjusted to display a single cardiac cycle. **A**, Group 1 fetuses. Rhythm was 2° AV block in subjects #14 and #15. Averaged waveforms were not computed for subject # 6 because the periods of sinus rhythm were brief. The LQTS type (1–3, CALM2, uncharacterized mutation (Un-C) or untested (Un-T)) are shown on the illustration. The T-waves exhibit a distinctive late-peaking morphology. T-wave humps near the end of the T-wave are evident in subjects #5, #10, and #17. **B**, Group 2 fetuses. All had normal postnatal QTc and none had an LQTS mutation or phenotype. AV indicates atrioventricular; fMCG, fetal magnetocardiography; LQTS, long QT syndrome; and QTc, corrected QT.

data from just the first session of each subject, the optimal threshold was unchanged and yielded sensitivity 86% and specificity 89%.

Baseline fHR in sinus rhythm was significantly lower in Group 1 (range 90–144 bpm, mean  $118.9 \pm 13.3$  bpm) than in

Group 2 (range 125–147 bpm, mean  $141.0 \pm 9.4$ ;  $P < 0.0001$ ; Figure 2). FHR reactivity, which cannot be reliably assessed before 28 weeks gestation, was low in 7 of 16 sessions of the Group 1 subjects and in 0 of 3 of the Group 2 subjects studied after 28 weeks gestation (Table).



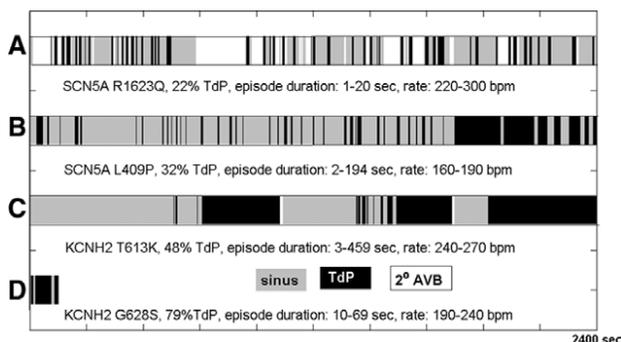
**Figure 2.** Fetal heart rates (FHRs) of Group 1 and Group 2 subjects, compared with percentiles for normal fetuses.<sup>7</sup> For reference, the 110 bpm FHR line across gestation is shown. For subjects with multiple visits, only the measurement from the first visit is shown.

### Fetal Rhythms

The 21 subjects in Group 1 showed VT or VT + 2° AV block (n=4), isolated 2° AV block (n=2), normal fHR in sinus rhythm (n=2), and isolated low fHR in sinus rhythm (n=13; Table). Of the 13 with isolated low fHR in sinus rhythm, only 2 had fHR ≤ 110 bpm, the commonly accepted obstetrical definition of fetal bradycardia. For the 4 subjects showing fetal TdP, the chronology of the various rhythms during the fMCG recording session is shown in Figure 3. The percent time in each rhythm was in the range 21–68% for sinus rhythm, 0.9–31% for 2° AV block, and 22–79% for TdP. The duration of TdP salvos (n=111) was in the range 1–462 s (mean 39 s). The ventricular rate during TdP was in the range 160–300 bpm and varied by as much as 30–70 bpm from episode to episode within the same subject.

### Patterns of Initiation and Termination of Torsades de Pointes

We observed complex and myriad rhythm patterns at initiation and termination of TdP (Figure 4). The most complex and varied were seen in subject #15 (SCN5A R1623Q). In both SCN5A and KCNH2 subjects, episodes of TdP were initiated



**Figure 3.** Chronology of LQTS rhythms (sinus rhythm–grey, 2° AV block–white, and TdP–black) during the fMCG session for the 4 fetuses with TdP. **A**, Subject #15. **B**, Subject #16. **C**, Subject #18. **D**, Subject # 6. The recording time in this subject was 120 s. AV indicates atrioventricular; fMCG, fetal magnetocardiography; LQTS, long QT syndrome; and TdP, Torsade de Pointes.

by a regular wide complex or aberrantly conducted rhythm, often involving QRS alternans or T-wave alternans, with a rate similar to narrow complex sinus rhythm (cycle length 418–488; Figure 4A–4C). TdP also followed a period of 2° AV block (Figure 4D). What was notably rare was the typical long–short sequence (ventricular ectopy) that initiates TdP seen after birth.

Rhythms occurring after spontaneous termination of TdP are shown in Figure 4E–4I. These rhythms included transient 2° AV block followed by sinus rhythm with QRS alternans (Figure 4E); 3° AV block (Figure 4F), pauses or narrow complex bradycardia with or without T-wave alternans (Figure 4G–4I). Ventricular fibrillation was not observed during any of the recordings.

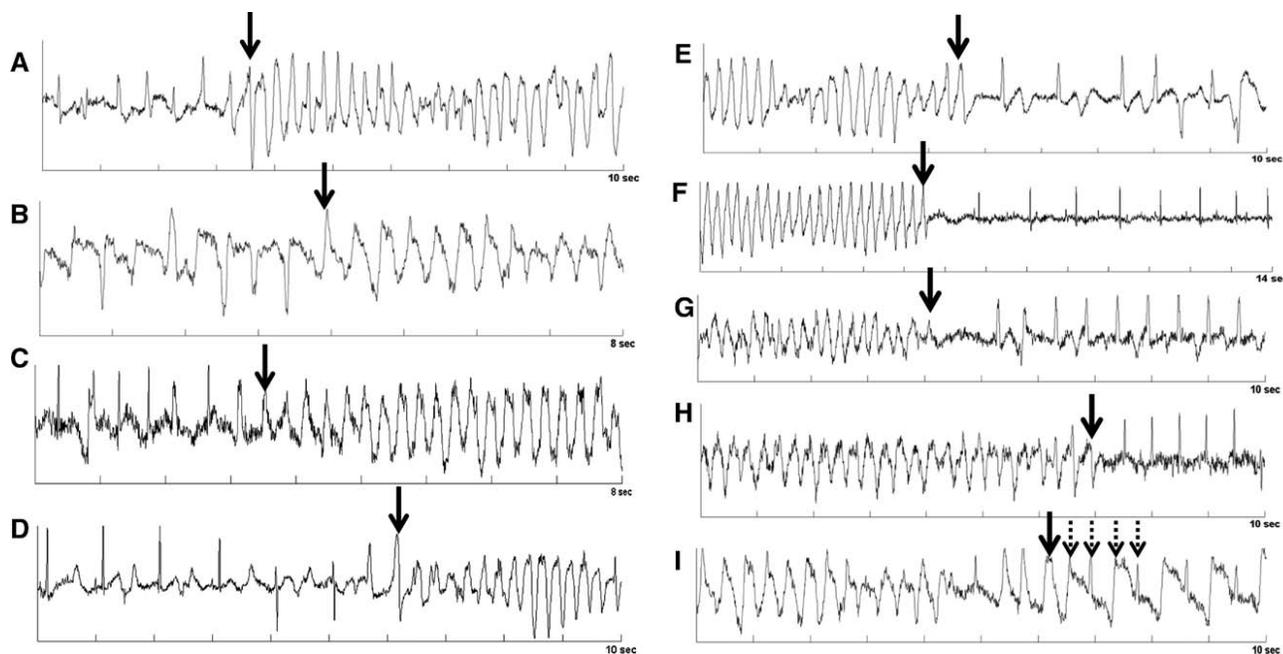
### Repolarization Characteristics

Episodes of macroscopic TWA conforming to an ABAB patterns were seen in 6 subjects (Figure 5). Discordance of T/QRS and large, late-peaking T-waves are prominent in these data. Subject #10 (Figure 5C) showed relatively mild TWA and did not have TdP. The other 5 showed prominent TWA and also QRS alternans. Importantly, they all had worse outcome: subjects #11, 15, 16, and 18 had fetal or neonatal TdP; subject #17 was delivered early because of new-onset multiform PVCs and R on T phenomenon diagnosed solely by fMCG. In this case the family history predicted significant risk of unstable arrhythmia. After pre-term delivery, the infant was started on, and responded to,  $\beta$ -blocker therapy. The most unusual tracing was seen in the 21-week fetus with a de novo SCN5A L409P mutation (subject #16; Figure 5B).<sup>11</sup> In this tracing, the T-wave is not well defined, and instead repolarization appears to occur continuously throughout the cardiac cycle. In contrast to adult TWA, the episodes of fetal TWA were typically brief and transient, often lasting 10 s or less. In addition, they were not strongly associated with elevated fHR. They could occur before or during fHR accelerations or during periods of quiescence.

An additional repolarization anomaly observed in 7 (33%) subjects in Group 1 was a marked increase in the T/QRS amplitude ratio during fetal movement (Figure 6). In normal subjects, fetal movement commonly alters the amplitude of the individual waveform components, but typically the ratio of the amplitudes shows relatively small changes and is equally likely to increase or decrease. In these 7 subjects, however, the ratio showed a consistent increase by a factor of 2 or more (Figure 6A). These subjects also showed little or no fHR reactivity (Figure 6C).

### Fetal Echocardiography, Fetal MCG, and Clinical Management

Fetal echocardiography and fMCG were usually concordant (Table), but the additional information from fMCG was significant in several cases. In 2 subjects, fMCG revealed rhythms not seen during serial echocardiograms: subject #18 (maternal KCNH2 mutation) had short runs of TdP that prompted substitution of nadolol with high dose propranolol and magnesium, and subject #17 (paternal KCNH2 mutation) was delivered because of multiform PVCs and R on T phenomenon (Figure 5E). Also, the definitive diagnosis of TdP in



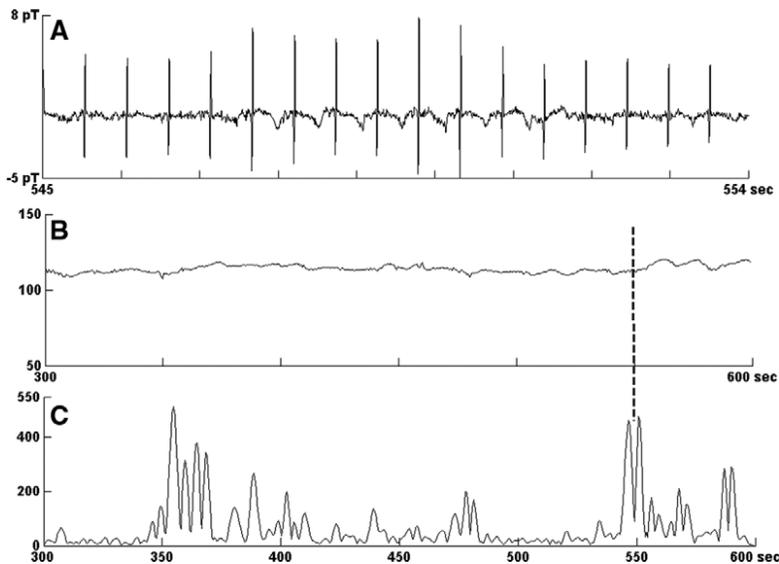
**Figure 4.** fMCG tracings at initiation (A–D) and termination (E–I) of TdP. The x axis tick marks are 1 s apart. First and last beats of TdP are marked by arrows. **A**, Wide complex (QRS duration 85 ms) regular rhythm (cycle length [CL] 488 ms) leads directly to a sustained run of TdP (CL 247 ms) in subject #15. The 2 beats before TdP show marked aberrancy. **B**, QRS alternans during wide complex (QRS duration 90 ms) regular rhythm (CL 418 ms) preceding spontaneous onset of a slow TdP (CL 351 ms) in subject #16. **C**, An aberrantly conducted QRS complex at same coupling interval as the narrow beats (CL 462 ms) initiates TdP (CL 272 ms) in subject #18. **D**, An aberrantly conducted beat in 2° AV block (arrow indicates conducted P-wave; ventricular CL 984, atrial CL 498 ms) leads to TdP (CL 238–281 ms) in subject #15. **E**, Second-degree AV block (atrial CL 1064, ventricular CL 540 ms) followed by sinus rhythm with QRS alternans in subject #15. **F**, Transient 3° AV block (ventricular CL 1111 ms; atrial CL 751 ms) after an episode of prolonged TdP (4 min) in subject #16. **G**, Pause (1.2 s) followed by narrow complex regular rhythm (CL 538 ms) and T-wave alternans in subject #15. **H**, Narrow complex regular rhythm (CL 487 ms) following TdP (CL 244 ms) in subject #18. **I**, Narrow complex regular rhythm (CL 487) with T-wave alternans. QRS complexes are shown by dashed arrows in subject #16. AV indicates atrioventricular; fMCG, fetal magnetocardiography; and TdP, Torsade de Pointes.

fetuses with VT allowed targeted prenatal treatment, including transplacental treatment with intravenous lidocaine and magnesium or oral  $\beta$ -adrenergic blocking agents that restored sinus rhythm (subject #6, 15)<sup>1,3</sup> or reduced the frequency of

TdP episodes (subject #18), thereby postponing delivery until fetal maturity. Lastly, rhythm and QTc duration derived from fMCG was used to risk-stratify prenatal and postnatal care: fetuses with normal fQTc were usually delivered at their



**Figure 5.** Examples of ABAB pattern of T-wave alternans (TWA). **A**, Subject #15 (SCN5A mutation and TdP). Notice that the widths of the QRS complexes alternate from beat to beat (QRS alternans). **B**, Subject #16 (de novo SCN5A L409P mutation and TdP). QRS alternans is present. The T-waves are highly abnormal T-waves and are not well defined but exhibit wide swings in amplitude and polarity. **C**, Subject #10 (uncharacterized mutation, no TdP). **D**, Subject #11 (CALM 2 mutation and postnatal TdP). This subject exhibits the most prominent beat-to-beat changes in T-wave morphology. The QRS complexes are biphasic and alternate polarity from beat to beat. **E**, Subject #17 (KCNH2 mutation, PVC, delivered at 34 weeks). This tracing shows a transition in the character of the TWA between the beginning and the end of the tracing. The second half of the tracing shows QRS alternans with alternating polarity from beat to beat and R on T phenomenon. **F**, Subject #18 (KCNH2 mutation, TdP). TWA and marked QRS aberrancy in alternating beats attributable to R-on-T phenomenon. PVC indicates premature ventricular contraction; and TdP, Torsade de Pointes.



**Figure 6.** Relationship between T/QRS amplitude ratio, fetal heart rate, and fetal movement in subject #9 (KCNQ1 mutation). The time scale is different for each panel. **A**, Nine-second rhythm tracing. The T/QRS amplitude ratio shows a transient increase between 547–551 s. **B**, Three hundred-second fetal heart rate (FHR) tracing. During the approximate period of 540–550 s (dashed line), which corresponds to the time of the T/QRS increase seen in **A**, the fHR tracing is flat. **C**, Three hundred-second actogram tracing. There is vigorous fetal movement around time 550 s (dashed line), corresponding to the time of the T/QRS increase seen in **A**, as well as at around time 360 s; however, as seen in **B**, the fHR is nonreactive.

referring hospitals; fetuses with prolonged fQTc were delivered at cardiac centers of excellence.

## Postnatal Evaluation

### ECG Cardiac Intervals and Rhythm

Of the 30 subjects, 29 had postnatal ECGs; 1 pregnancy (fetus #16) was electively interrupted. The values of QTc determined by fMCG and postnatal ECG were highly correlated ( $n=29$ ,  $r^2=0.494$ ,  $p<0.0001$ ). Prenatal fMCG and postnatal ECG were concordant for assessment of QTc prolongation with the exception of subject #22. This subject was referred for fMCG at 31 weeks' because of fetal bradycardia (fHR 104–125 bpm) and was found to have a prolonged fQTc (524 ms), accompanied by a late-peaking T-wave characteristic of fetal LQTS. Postnatally, however, the subject showed sinus bradycardia, a normal nQTc (424 ms), no LQTS mutation, and no Tdp or 2° AV block. Excluding this subject, there were no substantial differences between mean fetal and neonatal QRS duration (data not shown), mean fetal and neonatal heart rates ( $118.9\pm 13.3$  vs.  $117.2\pm 13.5$ ,  $P=0.67$ ), or mean fetal and neonatal QTc duration ( $565.3\pm 65.3$  vs.  $540.7\pm 53.4$ ;  $P=0.18$ ). Pre- and postnatal rhythm concordance was also high. Nearly all fetuses with isolated low fHR in sinus rhythm and all liveborn infants with fetal TdP had the same rhythm after birth. The 1 exception was Subject #11, who had a brief episode of 2° AV block in utero, but had both 2° AV block and TdP after birth.<sup>12</sup>

### Genetic Testing of Subjects and Family Members

Genetic testing was performed on 27 of 30 neonatal subjects (Table). All 9 subjects in Group 2 (normal fetal and neonatal QTc) were tested and none had an LQTS mutation. Of the 21 Group 1 subjects, 17 had a positive mutation: 9 had KCNQ1 mutations, 5 had KCNH2 mutations, 2 had SCN5A mutations, and 1 had a CALM2 mutation. One subject (#10) did not have a mutation in a known LQTS susceptibility gene, and 3 subjects were not tested.

If the fetus was a proband ( $n=7$ ), ECG screening for LQTS was recommended to first-degree relatives. Parents of 1 subject refused to be tested because of insurability concerns, members of 3 families had normal ECGs, and 6 members of

3 families had abnormal ECGs. These asymptomatic family members (1 father, 2 mothers, and 3 siblings) had the same mutation as that of the proband.

### Genotype/Phenotype Correlations

No significant differences in fetal HR or fetal QTc duration could be detected between LQTS mutation type; however, the numbers were too small to draw meaningful conclusions. Associations between the most severe phenotypes—QTc $\geq 620$  ms, TdP, and TWA—and specific mutations were not evident; however, these phenotypes were not seen in any fetal subject with a KCNQ1 mutation. This is of interest because TWA was first noticed in an LQT1 subject.<sup>13</sup>

## Discussion

This is the first study to document the electrophysiological characteristics of fetal LQTS and to evaluate the accuracy of fMCG for identifying congenital LQTS in a sizable population of at-risk fetuses. The main findings were as follows: (1) Using a threshold of QTc $> 490$  ms, fMCG was able to identify the fetuses with LQTS with high accuracy (89% sensitivity, 89% specificity). This threshold value happens to correspond to the upper bound of the 95% prediction interval of QTc in normal fetuses.<sup>14</sup> (2) Perinatal TdP was associated with markedly prolonged QTc ( $\geq 620$ ms) and was accompanied by multiple, uncommon rhythms: 2° atrioventricular block, TWA, and QRS alternans; however, TdP did not degenerate into ventricular fibrillation, even when intermittent TdP was present for days or even weeks. (3) Fetal TdP sometimes initiated with a long-short pattern, but most often it initiated with an aberrantly conducted beat with little or no cycle lengthening. The predominance of this initiation pattern may be unique to the fetus. Below we discuss these findings and consider their clinical implications.

As verified by genetic testing, the sensitivity and specificity of fMCG for the diagnosis of LQTS in utero was high. The concordance between fMCG and postnatal ECG was also high, both for QRS and QTc measurements and for rhythm assessment. In addition to fQTc prolongation, another sentinel marker of fetal LQTS was the late-peaking T-wave

morphology, and the occasional appearance of T-wave humps. In addition, some LQTS subjects showed a pronounced increase in T-wave amplitude in association with fetal movement, which we speculate may mimic a stress test. These distinctive characteristics were especially helpful at early gestational ages when fetal T-waves tend to be flat.

Our study demonstrates that QTc prolongation, the defining characteristic of LQTS, manifests early in life—just how early remains unknown, but our data support the inference that it is commonly present after mid-gestation. One LQTS subject (#21), however, had a normal fQTc with normal T-wave morphology in the first session at 27 weeks' and a prolonged fQTc with late-peaking T-wave morphology in 2 subsequent sessions at 29 and 34 weeks. This suggests that in some subjects QTc prolongation does not develop until later in pregnancy, and that a single screening at an early gestational age may fail to detect a small percentage of cases of LQTS.

The prognostic value of fQTc assessment was demonstrated by the finding that of the 6 fetuses with longest QTc, 4 (QTc  $\geq$  620 ms) had fetal TdP, 1 (QTc = 633 ms) had neonatal TdP, and 1 (QTc = 610 ms) was delivered at 34 weeks after fMCG revealed the ominous findings of multiform PVCs and multiple episodes of R on T phenomenon.

Our fHR data agree with those of Mitchell and co-workers, who showed that LQTS is strongly associated with fHR  $<$  3<sup>rd</sup>%. In addition, we studied fetuses with a family history of LQTS that do not carry the mutation and showed that they have fHR  $\geq$  3<sup>rd</sup>%. Along with low baseline heart rate, the prevalence of nonreactive heart rate patterns in the LQTS fetuses documented in this study is compatible with lower-than-normal right sympathetic cardiac activity or a blunted response to sympathetic drive, as seen postnatally.<sup>15</sup> Sympathetic imbalance is believed to play a critical role in triggering lethal arrhythmias in LQTS.<sup>16</sup>

Among the most striking rhythm patterns were the episodes of TWA, which commonly showed large, late peaking T-waves, QRS-T discordance, and QRS alternans. TWA is a critically important marker of cardiac instability and severe disease.<sup>13</sup> QRS alternans, however, is not considered an indicator of cardiac instability, nor is it normally associated with congenital LQTS. In our subjects it occurs because extreme QTc prolongation in conjunction with the higher heart rate of the fetus results in substantial overlap of ventricular depolarization and repolarization, as exemplified by R on T phenomenon, which in the presence of TWA produces alternation in QRS morphology as a result of aberrancy. The combination of prominent TWA and QRS alternans was strongly associated with a poorer prognosis. This is not surprising because QRS alternans occurs in the most severe cases when QTc is markedly prolonged and TWA is present. In addition, however, aberrancy associated with QRS alternans appears to be an important mechanism of initiation of TdP.

Unlike what is commonly seen in the postnatal patient, most of the episodes of TdP were not pause-dependent. TdP usually occurs after a pause that delays repolarization. This can induce early afterdepolarizations and enable the formation of a PVC that initiates TdP, resulting in the long-short

pattern that is a hallmark of TdP. In our subjects, however, most of the initiations involved various forms of aberrantly conducted beats with little or no cycle length changes. We therefore speculate that reentry, facilitated by bundle-branch block, was an important mechanism of initiation. Its predominance in the fetus may result from the prevalence of aberrancy, as exemplified by QRS alternans, relative to what is seen postnatally. In addition, initiation by the long-short pattern may be hampered by the strong rate dependence of early after depolarizations, which are less likely to reach critical threshold at the higher heart rates of the fetus.

Another unexpected finding was that ventricular fibrillation was not seen, even when TdP recurred often, was present continuously for many minutes, or occurred intermittently for days and even weeks. Postnatally, it is commonly observed that TdP degenerates into ventricular fibrillation if it persists for more than several minutes. We speculate that the fetus does not develop severe myocardial hypoxia because the maternal/fetal circulation is protective or is better adapted to tolerate hypoxia because of the lower ambient pO<sub>2</sub> in utero. Although we did not see ventricular fibrillation, 2 fetuses (gestational ages 21 and 31 weeks) with SCN5A mutations developed heart failure. Ventricular fibrillation could still occur unobserved, because lethal rhythms are exceedingly brief. Without molecular autopsy, the resultant deaths would be classified as stillbirths or sudden infant death syndrome (SIDs). A recent study of stillborn infants showed a 3.3% incidence of mutations in LQTS susceptibility genes and an 8.8% incidence of genetic variants that lead to dysfunctional LQTS-associated ion channels in vitro,<sup>17</sup> supporting the hypothesis that LQTS can cause stillbirths as well as sudden infant death syndrome.<sup>18</sup>

Fetal MCG results altered antenatal management of the mother and fetus, the timing and location of delivery, and the anticipation of postnatal management, regardless of the family history and independent of LQTS rhythm. Mothers of fetuses with suspected LQTS did not receive QT prolonging medications such as oxytocin, erythromycin, or ondansetron during pregnancy, labor, or delivery. Such management may have averted harm not only to the fetus but also to the pregnant mother unexpectedly found to have LQTS after undergoing ECG screening because of her fetus's MCG results. MCG also enabled definitive diagnosis of TdP, despite its transient and variable nature, which prompted appropriate, effective in utero pharmacologic therapy. Importantly, TdP was detected in 18% of subjects with an LQTS family history, but negative echocardiographic surveillance before fMCG evaluation. These subjects were successfully delivered at cardiac centers of excellence.

Finally, LQTS was diagnosed in 5 subjects with an isolated finding of fHR  $<$  3<sup>rd</sup>% and in 6 unsuspecting members of 3 fMCG-diagnosed LQTS families. These results suggest that, in addition to a positive family history or findings of complex rhythm in utero, fetuses with low-for-gestational-age heart rates should be monitored for the development of LQTS rhythms and considered for fMCG screening.

In conclusion, QTc assessment by fMCG was shown to have diagnostic value for identification of fetuses with LQTS and prognostic value for prediction of a severe phenotype. In

addition, fMCG was invaluable for the detection and definitive diagnosis of TdP. fMCG findings not only prompted successful in utero pharmacological treatment to restore sinus rhythm and postpone the delivery of a premature fetus, but also guided anticipatory neonatal care. The ability to recognize LQTS in the fetus and to effectively treat TdP in utero can be lifesaving.

### Sources of Funding

This work was supported by National Institutes of Health grant R01 HL63174.

### Disclosures

None.

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### CLINICAL PERSPECTIVE

Long QT syndrome (LQTS) is among the most common causes of sudden cardiac death in the young. Although its role in sudden infant death syndrome has been known for more than a decade, a very recent study by Crotti and colleagues suggests that LQTS may also be responsible for >10% of unexplained fetal death. This finding implies that many lives might be saved if LQTS could be accurately diagnosed and effectively treated in utero. Our study demonstrates that both are possible. Using fetal magnetocardiography (fMCG), the magnetic analog of ECG, we show that fetal QTc has diagnostic value for identification of fetuses with LQTS and prognostic value for prediction of a severe phenotype. In addition, fMCG was invaluable for definitive detection of the signature lethal rhythm of LQTS, Torsades de Pointes. The fMCG findings not only prompted successful in utero pharmacological treatment to restore sinus rhythm and postpone the delivery of a premature fetus, but also guided anticipatory neonatal care. Because of the known association between LQTS and low heart rate, some fetuses with an isolated finding of low-for-gestational-age heart rate (< 3%) were referred for fMCG testing and were found to have LQTS. This led to the identification of LQTS in several unsuspecting first-degree relatives. Currently, fMCG is not readily accessible to clinicians because of the cost and complexity of the instrumentation; however, a new technology, based on atomic magnetometers, has the potential to rectify this situation.

## In Utero Diagnosis of Long QT Syndrome by Magnetocardiography

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*Circulation*. 2013;128:2183-2191

doi: 10.1161/CIRCULATIONAHA.113.004840

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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